REMARKS

In view of the foregoing amendments, reconsideration and withdrawal of the outstanding Office Action rejections are respectfully requested. Claim 295 has been amended by incorporating the subject matter of claim 309 and claim 309 has therefore been cancelled. Claims 313 and 319 have been amended only to correct antecedent basis issues as suggested in the Office Action. No new matter has been added.

The amendments are made to put the application in better condition for allowance or appeal. Thus, Applicants respectfully request that they be entered and favorably considered.

Response to Objections to Specification

The specification was objected to for lacking reference to sequence identifiers in Figure 11a. A replacement Figure 11a is being submitted that includes sequence identifiers. Accordingly, Applicants respectfully request that the objections be withdrawn.

Response to Rejections under 35 U.S.C. § 112

Claims 313 and 319 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Patent Office asserts that the phrases "the site of the wound" and "said composition" lack antecedent basis. By the present amendment, claims 313 and 319 have been amended in view of the Examiner's comments. Favorable reconsideration and withdrawal of the rejection are respectfully requested.

Response to Rejections under 35 U.S.C. § 102

Claims 295-297, 301, 302, 304, 310, 313-315, and 324 were rejected under 35 U.S.C. § 102(b) as being anticipated by Esteve as evidenced by Horecker (U.S. 4,388,234).

In the Office Action, it is asserted that Esteve discloses that a composition containing thymus extract from bovines that contains 'thymosine' is effective to help repair modifications of the internal structure of skin cells affected by UV radiation. Although Esteve does not disclose the components of the thymus extract other than mentioning "thymosine," the Patent Office asserts that Horecker discloses that thymus extract contains thymosin alpha-1 and thymosin beta 4. Accordingly, the Office Action asserts that Esteve discloses administering thymosin beta 4 to human patients to repair modifications of skin cells affected by UV radiation.

Insofar as this rejection could apply to the present claims, it is respectfully traversed.

The subject matter of claim 309, which was not rejected as being anticipated by Esteve has been incorporated into independent claim 295. Therefore, without acquiescing to the proprieties of the Office Action rejections, Applicants respectfully submit that the rejection has been rendered moot and request that it be withdrawn.

If the prior art reference merely discloses a genus and the claim at issue recites a species of that genus, the issue of anticipation turns on whether the genus was of such a defined and limited class that one of ordinary skill in the art could "at once envisage" each member of the genus. *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*,

471 F.3d 1369, 1376 (Fed. Cir. 2006). With regard to claim 295 as originally presented, Applicants respectfully submit that a person of ordinary skill in the art reading Esteve could not have "at once envisaged" that Esteve disclosed thymosin beta 4. Esteve mentions "thymosine." It is unclear what is meant by "thymosine." Further, Horecker discloses components of Thymosin Fraction 5, whereas Esteve merely mentions a thymus extract from young bovines. A person of ordinary skill in the art at the time of the invention would not have understood Esteve's mention of "thymosine" as disclosing thymosin beta 4 or thymosin fraction 5. There is no evidence on the record supporting such a reading of Esteve. Even more, the compositions of Esteve contain 10%, 15%, or 5% of the active complex, which contains only 20% of a thymus extract. Thus, even if the thymus extract of Esteve contained some small amount thymosin beta 4, which is not evidenced by the citations of record, there is no evidence that the thymosin beta 4 was present in an "effective amount" as recited in original claim 295 or in the amended claims. Indeed, the active complex of Esteve contained a number of active ingredients including 50% of various vitamins and 30% milk thistle extract, in addition to 20% of the thymus extract. Thus, a person of ordinary skill in the art reading Esteve would not have known 1) whether the composition contained any thymosin beta 4 and 2) whether it contained an effective amount of thymosin beta 4. Thus, the rejection, as applied to claim 295 as originally presented, was unfounded.

Response to Rejections under 35 U.S.C. § 103

Claims 295-298, 301, 302, 304, 309, 310, 313-315, 317-322, and 324 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldstein (U.S. 5,578,570) and Lai (U.S. 5,358,703) and Palladino (U.S. 5,055,447). Applicants respectfully disagree and traverse the rejection.

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Moreover, as the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)).

The Federal Circuit has repeatedly emphasized that the objective indicia constitute "independent evidence of nonobviousness." *Pressure Prods. Med. Supplies, Inc. v. Greatbatch Ltd.*, 599 F.3d 1308, 1319 (Fed. Cir. 2010). Indeed, objective indicia "may often be the most probative and cogent evidence of nonobviousness in the record." *Ortho-McNeil Pharm. V. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008); *see also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985) (Objective indicia "may be the most pertinent, probative, and revealing evidence available to the decision maker in reaching a conclusion on the

obviousness/nonobviousness issue."). Such evidence "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984). The objective indicia "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966).

> Simply because the technology can be easily understood does not mean that it will satisfy the legal standard of obviousness. In fact, objective consideration of simple technology is often the most difficult because, once the problem and solution appear together in the patent disclosure, the advance seems self-evident. Instead, the proper analysis requires a form of amnesia that "forgets" the invention and analyzes the prior art and understanding of the problem at the date of invention.

Mintz v. Dietz & Watson, Inc., No. 2010-1341, slip op. at 13 (Fed. Cir. May 30, 2012) (requiring that "common sense" be articulated, by avoiding the use of the patent itself in defining the problem the invention solves, and by emphasizing the need to analyze the objective indicia of nonobviousness).

Here, the Patent Office acknowledges that Goldstein does not reduce to practice using topical administrations and does not disclose use of transforming growth factor beta.

Independent claim 295 recites "[i]n a method for treating tissue in a human with thymosin beta 4 (Tβ4), the method comprising targeting cells of said tissue to be treated prior to administration of said Tβ4, then administering said Tβ4 to said targeted tissue so as to promote repair and revitalization of said tissue, wherein said Tβ4 is

administered in an amount effective to promote repair and revitalize said tissue, wherein said human is suffering from a wound." Goldstein explains that septic shock is a condition in which infection is widely disseminated in many areas of the body through the blood. Col. 1, lines 24-27. The Tβ4 treatment described in Goldstein aims to reduce blood levels of pathological mediators of bacteria-induced lethality to obstruct the sepsis cascade. Col. 2, lines 31-36. Because the treatment is administered to reduce blood levels of pathological mediators of bacteria-induced lethality, Goldstein does not disclose or suggest the steps of targeting cells of tissue to be treated prior to administration of said Tβ4, then administering said Tβ4 to said targeted tissue so as to promote repair and revitalization of said tissue. Therefore, Applicants submit that the cited combination does not suggest the subject matter of independent claim 295 at least because none of the references treat tissue in a human suffering from a wound, target cells of tissue to be treated prior to administration of Tβ4, administer Tβ4 to the targeted tissue so as to promote repair and revitalization of the tissue, or administer Tβ4 in an amount effective to promote repair and revitalize the tissue in a human suffering from a wound. Neither Palladino nor Lai remedy the deficiencies of Goldstein because these references, while related to treating septic shock, are irrelevant to the presently claimed method and patient population. The failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103. Accordingly, Applicants respectfully request that the rejection be withdrawn. Further, the dependent claims should be free of Goldstein, Lai, and Palladino for the same reasons as the base claim and further due

to the additional features that they recite.

Recently, the Federal Circuit again confirmed that, where a person of ordinary skill would not have drawn a connection a claimed treatment and a different known treatment, process claims drawn to using a known compound for the claimed treatment are not rendered obvious by the known treatment using the same compound. *See Eli Lilly & Co. v. Teva Pharmaceuticals USA, Inc.*, 619 F.3d 1329, 1338 (Fed. Cir. 2010) (finding a patent for treating autoimmune disease using raloxifene did not render a patent drawn to treating osteoporosis using raloxifene obvious because no credible connection between the diseases was established). As discussed above, it is clear that a person of ordinary skill would not have recognized any connection between the septic shock (which is what the cited art teaches) and promoting repair and revitalization of tissue in a human suffering from a wound (which is what is claimed). Here, because the facts are analogous to those in *Eli Lilly*, the obviousness rejections are clearly erroneous and should be withdrawn.

The Office Action, at page 12, third paragraph, states that "MPEP 2121 states that prior art is presumed enabled. It is noted that Goldstein is an issued patent. If applicants (i.e. Goldstein is listed as an inventor of the instant application) are of the position that their own issued patent is not valid applicants may provide evidence of such." This argument is not well-taken. In fact, the Office Action comments clearly demonstrate both that there is a misunderstanding of the relevant law and that the provisions of the MPEP have been taken out of context. In full, MPEP § 2121(I) provides that "[w]hen the reference relied on expressly anticipates or makes obvious all

of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability." (citing *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980)). Thus, not only is the presumption rebuttable, but the presumption is also **only** valid where "the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention." Applicants respectfully submit that the references relied on do not expressly anticipate the claims because the anticipation rejection over Goldstein was withdrawn by this Office Action. Furthermore, Applicants respectfully submit that the references relied on do not make obvious all of the elements of the claimed invention for at least the above reasons. In such a case, the MPEP provides that there is no need for applicants to rebut the presumption, but applicants respectfully point out that the presumption is not absolute as the Office Action seems to declare.

Moreover, it is not the Applicants' argument that Goldstein is not enabled or not valid as incorrectly characterized on page 12 of the Office Action. Rather, it is the Applicants' argument that Goldstein's disclosure would not have enabled a person of ordinary skill in the art to practice the method claimed in this application because Goldstein's disclosure is simply not related to a method for treating tissue in a human with thymosin beta 4 (Tβ4), the method comprising targeting cells of said tissue to be treated prior to administration of said Tβ4, then administering said Tβ4 to said targeted tissue so as to promote repair and revitalization of said tissue, wherein said Tβ4 is administered in an amount effective to promote repair and revitalize said tissue, wherein said human is suffering from a wound.

The combination of cited references simply do not relate to, suggest, or even hint at a method for treating tissue in a human with thymosin beta 4 (Tβ4), the method comprising targeting cells of said tissue to be treated prior to administration of said Tβ4, then administering said Tβ4 to said targeted tissue so as to promote repair and revitalization of said tissue, wherein said Tβ4 is administered in an amount effective to promote repair and revitalize said tissue, wherein said human is suffering from a wound. Indeed, the disclosures Goldstein, Lai, and Palladino relate to treating septic shock and have nothing to do with treating tissue in a human suffering from a wound with thymosin beta 4 (Tβ4), by targeting cells of said tissue to be treated prior to administration of said Tβ4, then administering said Tβ4 to said targeted tissue so as to promote repair and revitalization of said tissue, wherein said Tβ4 is administered in an amount effective to promote repair and revitalize said tissue, wherein said human is suffering from a wound. Indeed, Goldstein is related to stopping the sepsis cascade by administering TB4 simultaneously or within 5 minutes of administration of the endotoxin that can cause sepsis. The working examples in Goldstein mention making a puncture wound using a 16-gauge needle into the anti-mesenteric surface of the cecum of rats so as to introduce fecal matter into the peritoneal cavity of the rats to cause sepsis. *See* Example 5. However, this disclosure in Goldstein merely describes an experimental animal model intended to cause sepsis in rats by producing a hole in the cecum through which sepsis causing fecal matter could travel and does not describe that the patient population to be treated by the method of Goldstein is simply rats "having a wound." Moreover, Goldstein does not disclose or suggest the patient

population of a "human having a wound." The disclosures of the cited references did not motivate or enable a person of ordinary skill in the art at the time of the invention to treat the claimed patient population, or to practice the steps according to the presently claimed method.

A person of ordinary skill in the art aware of Goldstein, Lai, and Palladino would not have been motivated to treat a human suffering from a wound with thymosin beta 4 (Tβ4), by targeting cells of said tissue to be treated prior to administration of said Tβ4, then administering said Tβ4 to said targeted tissue so as to promote repair and revitalization of said tissue, wherein said Tβ4 is administered in an amount effective to promote repair and revitalize said tissue. Not only did the combination of references relied upon not "make obvious all of the elements of the claimed invention," which is already fatal under MPEP § 2121(I), but any presumption of operability for these references with regard to the presently claimed method has been rebutted by the above arguments as well as Applicants' previously-filed arguments. Favorable reconsideration and withdrawal of this rejection are respectfully requested for these further reasons.

As discussed in Applicants' previous response, there is no indication in Goldstein that the sepsis cascade has progressed to the stage where tissue damage sets in and that Tβ4 treats the tissue damage at this stage. Moreover, there is no suggestion in Goldstein that tissue damage has occurred and can be treated by administering Tβ4. Indeed, neither Goldstein nor Lai provide such evidence or suggestions. Moreover, Lai discloses that septic shock is "manifested by hypotension, a reduced response to vasoconstrictors…and multi-organ failure." (Lai, col. 1:41-45.) If one were to accept

the logical reasoning applied in the Office Action on its face, Goldstein can also be said to anticipate or render obvious methods of treating one or more of hypotension, a reduced response to vasoconstrictors, and multi-organ failure in any animal using Tβ4 because Lai discloses that septic shock is manifested by these conditions as well. The logic employed in the Office Action fails because the Supreme Court has stated, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)). The knowledgeable person of skill in the art must have had both a reason to combine the elements "in the fashion claimed" and a predictability of the result. *See KSR*, 550 U.S. at 417-418; *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). For the same reasons that the above logic, if it was directed against claims drawn to methods of treating hypotension, a reduced response to vasoconstrictors, or multi-organ failure, fails to satisfy the tests under 35 U.S.C. §§ 102 and 103, and such an application of Goldstein would not be upheld by a well-informed examiner, Board, or court, the present rejections based on Goldstein are also improper. Here, the Patent Office has failed to carry its burden of demonstrating that 1) Goldstein provides an enabling disclosure for treating tissue in a human suffering from a wound, 2) tissue damage is an inherent condition that was treated by Goldstein, or 3) a person of ordinary skill would have had reason to attempt to carry out the claimed process, and would have had a reasonable expectation of success. Accordingly, Applicants respectfully request that the rejection be withdrawn for these additional reasons.

In view of the foregoing, Applicants respectfully submit that the independent claim patentably defines the present invention over the citations of record. Further, the dependent claims should also be allowable for the same reasons as their respective base claims and further due to the additional features that they recite.

Response to Provisional Double Patenting Rejections

Various combinations of previously pending claims remained provisionally rejected under the doctrine of non-statutory double patenting over separate co-pending patent applications. Applicants continue to request that all provisional rejections on grounds of double patenting be held in abeyance until such claims have been indicated to be allowable and it becomes possible to determine whether claims directed to the same invention or an obvious variant thereof would be issued in more than one patent.

Conclusions

In light of the foregoing, Applicants submit that all outstanding non-provisional rejections have been overcome. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all the outstanding non-provisional rejections. Early and favorable action is awaited.

The Commissioner is hereby authorized to charge any fees and to credit any overpayments that may be required with respect to this paper to Counsel's Deposit Account No.02-2135.

Respectfully submitted,

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